HETEROCYCLES, Vol 27, No. 7, 1988

ENANTIOSELECTIVE REDUCTION OF RACEMIC EPOXIDES WITH THE CHIRAL 9-ALKOXY-9-BORABICYCLO[3.3.1]NONANE-POTASSIUM HYDRIDE AND CHIRAL POTASSIUM 9-ALKOXY-9-BORATABICYCLO[3.3.1]NONANE SYSTEMS

Jin Soon Cha,[•] Kwang Woo Lee, Mal Sook Yoon, and Jae Cheol Lee

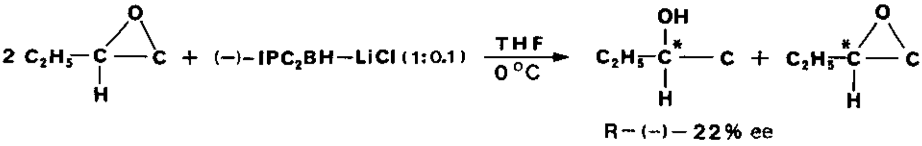
Department of Chemistry, Yeungnam University, Gyongsan 713-800, Korea

Nung Min Yoon

Department of Chemistry, Sogang University, Seoul 121-110, Korea

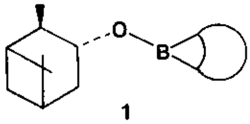
Abstract - The chiral 9-alkoxy-9-borabicyclo[3.3.1]nonane (**1** and **2**)-potassium hydride and chiral potassium 9-alkoxy-9-boratabicyclo[3.3.1]nonane (**3** and **4**) systems were applied to the enantioselective reduction (resolution) of representative racemic epoxides, such as 1,2-epoxybutane, 1,2-epoxyoctane, 3,3-dimethyl-1,2-epoxybutane, and styrene oxide. The enantioselectivity by **1**-KH and **2**-KH systems was in the range of 9.8-46.3% ee. The corresponding chiral borohydrides, **3** and **4**, resolved racemic epoxides examined in the range of 9.8-43.3% ee. All the reduction products were consistently enriched in the enantiomer with levorotation.

Our first report on the enantioselective reduction of racemic 1,2-epoxybutane with the chiral (-)-diisopinocampheylborane ((-)-IPC$_2$BH)-lithium chloride (1:0.1) system to give R-(-)-2-butanol in 22% ee at 0°C (eq 1)[1] indicated the new methodology for the resolution of racemic heterocyclic compounds.[2] We have interpreted these results as the chiral organoborane discriminates R- and S-enantiomers at the step of coordination to the hetero atom of ring followed by reduction.

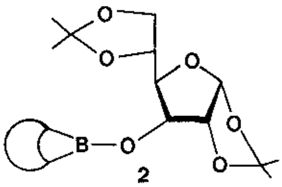


(1)

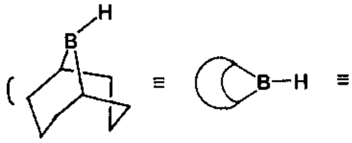
On this basis, we utilized the chiral R$_3$B-KH and chiral KR$_3$BH systems using readily available chiral auxiliaries in the enantioselective reduction of various racemic epoxides in the hope to find out the mechanistic importance and to establish the proper system for such resolution.
We selected two chiral borinic esters, such as 9-isopinocampheyloxy-9-borabicyclo[3.3.1]nonane (9-O-IPC-9-BBN) (**1**) and 9-O-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose-9-borabicyclo[3.3.1]nonane (9-O-DIPGF-9-BBN) (**2**), prepared by treating the corresponding alcohols with 9-BBN. These chiral borinic esters are readily converted to the corresponding potassium 9-alkoxy-9-boratabicyclo[3.3.1]nonanes, K 9-O-IPC-9-BBNH (**3**) and K 9-O-DIPGF-9-BBNH (**4**), by treatment of **1** and **2**, respectively, with excess potassium hydride (eq 2). We applied these four systems (**1**-KH, **2**-KH, **3**, **4**) to the enantioselective reduction of representative racemic epoxides, such as 1,2-epoxybutane, 1,2-epoxyoctane, 3,3-dimethyl-1,2-epoxybutane, and styrene oxide. The **1**-KH and **2**-KH systems are believed to proceed



1

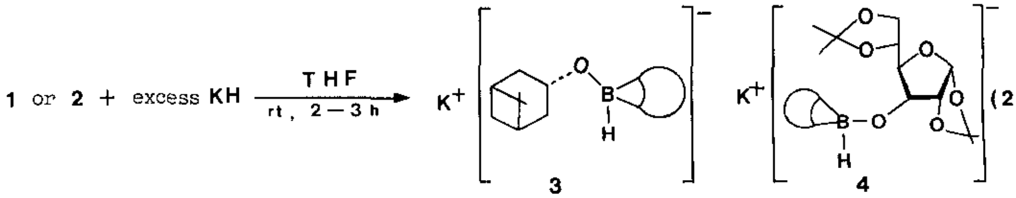


2



(≡ ≡ 9-borabicyclo[3.3.1]nonane)

via the initial enantioselective coordination of the chiral borane on the epoxy oxygen followed by reduction, while the borohydrides **3** and **4** , directly attacks the epoxy ring enantioselectively (Scheme 1). Actually, it is our major interest to evaluate the role of steps of enantioselective coordination and enantioselective reduction.



(2)

The enantioselective reaction was carried out by either the treatment of 2 equiv of epoxide with 1 equiv of 9-OR*-9-BBN followed by reduction with excess KH, or the treatment of 2 equiv of epoxide with 1 equiv of K 9-OR*-9-BBNH, both at 0°C. The reduction went to completion in 7-15 h and the isolated yields of alcohols are 70-85%, as summarized in Table I-IV.

Scheme 1

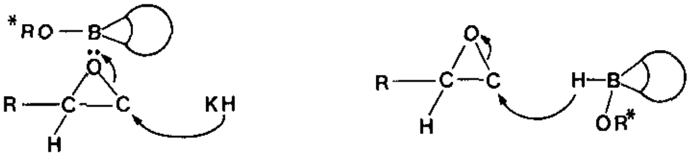


Table I. Enantioselective Reaction of Representative Racemic Epoxides with the 9-O-IPC[a]-9-BBN (**1**)-*KH System in Tetrahydrofuran at 0°C*

Epoxide	Product	Yield (%)	$[\alpha]_D^{22}$ degree	% ee[b] (Absolute config.)	Correction[e] % ee
1,2-Epoxybutane	2-Butanol[c]	76	-3.40	25.2 (R)	26.4
	2-Butanol[d]	78	+3.35	24.8 (S)	26.0
1,2-Epoxyoctane	2-Octanol[c]	85	-3.94	39.8 (R)	41.7
	2-Octanol[d]	87	+3.87	39.0 (S)	40.8
3,3-Dimethyl-1,2-epoxybutane	3,3-Dimethyl-2-butanol[c]	81	-2.32	28.6 (R)	29.9
Styrene oxide	1-Phenylethanol[c]	75	-4.03	9.4 (S)	9.8

[a] 95.5% ee (-)-isopinocampheol ($[\alpha]_D^{23}$ -34.1°) used.

[b] Based on the maximum $[\alpha]_D$ values reported : R-2-butanol[3] -13.5° ; S-2-octanol[4] +9.9° ; R-3,3-dimethyl-2-butanol[5] -8.1° ; R-1-phenylethanol[6] +42.85°.

[c] From the reduction of epoxide with the system.

[d] From the reduction of distillate of the unreacted with $LiAlH_4$.

[e] Corrected values for 100% ee (-)-isopinocampheol.

The optical yields of alcohols obtained by the **1**-KH system, as summarized in Table I, appear to be variable with the structure of epoxides. The ee values for the aliphatic series examined are in the range of 26.0-41.7%, however the value for aromatic epoxide is only 9.8%. On the other hand, the absolute configuration of alcohol products are consistently rich in R for the aliphatic series and S for the aromatic one with a constant levorotation.[3-6]

Table II. Enantioselective Reaction of Representative Racemic Epoxides with the 9-O-DIPGF[f]-9-BBN (**2**)-KH System in Tetrahydrofuran at 0°C

Epoxide	Product	Yield (%)	$[\alpha]_D^{22}$ degree	% ee[b] (Absolute config.)
1,2-Epoxybutane	2-Butanol[c]	78	-4.40	32.6 (R)
	2-Butanol[d]	75	+4.12	30.5 (S)
1,2-Epoxyoctane	2-Octanol[c]	82	-4.58	46.3 (R)
	2-Octanol[d]	83	+4.42	44.6 (S)
3,3-Dimethyl-1,2-epoxybutane	3,3-Dimethyl-2-butanol[c]	75	-2.53	31.2 (R)
Styrene oxide	1-Phenylethanol[c]	82	-10.6	24.7 (S)

f) $[\alpha]_D^{20}$ -18.5° (c=5, H_2O), 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose used.

b)- d) See corresponding footnotes in Table I.

The **2**-KH system achieves the enantioselectivity in the range of 24.7-46.3% ee, being significantly higher than that of the **1**-KH system, as summarized in Table II. However, the trend both for the ee value and absolute configuration is exactly same in both cases.

Table III. Enantioselective Reaction of Representative Racemic Epoxides with K 9-O-IPC[a]-9-BBNH (**3**) in Tetrahydrofuran at 0°C

Epoxide	Product	Yield (%)	$[\alpha]_D^{22}$ degree	% ee[b] (Absolute config.)	Correction[e] % ee
1,2-Epoxybutane	2-Butanol[c]	78	-3.33	24.7 (R)	25.9
	2-Butanol[d]	80	+3.19	24.3 (S)	25.4
1,2-Epoxyoctane	2-Octanol[c]	84	-3.68	37.2 (R)	39.0
	2-Octanol[d]	83	+3.61	36.5 (S)	38.2
3,3-Dimethyl-1,2-epoxybutane	3,3-Dimethyl-2-butanol[c]	81	-1.73	21.4 (R)	22.4
Styrene oxide	1-Phenylethanol[c]	78	-3.94	9.2 (S)	9.6

a)- e) See corresponding footnotes in Table II.

Table IV. Enantioselective Reaction of Representative Racemic Epoxides with K 9-O-DIPGF[f]-9-BBNH (**4**) in Tetrahydrofuran at 0°C

Epoxide	Product	Yield (%)	$[\alpha]_D^{22}$ degree	% ee[b] (Absolute config.)
1,2-Epoxybutane	2-Butanol[c]	77	-3.67	27.2 (R)
	2-Butanol[d]	70	+3.90	28.9 (S)
1,2-Epoxyoctane	2-Octanol[c]	74	-4.29	43.3 (R)
	2-Octanol[d]	75	+4.09	41.3 (S)
3,3-Dimethyl-1,2-epoxybutane	3,3-Dimethyl-2-butanol[c]	78	-2.16	26.6 (R)
Styrene oxide	1-Phenylethanol[c]	81	-9.38	21.9 (S)

b)- f) See corresponding footnotes in Table II.

The results achieved by **3** and **4** , as shown in Table III and IV, provide an interesting feature, even though a similar trend both for the ee value and absolute configuration is apparent. Thus, the enantioselectivity by the chiral borohydride, which has no vacant orbital for coordination, toward racemic epoxides is constantly lower than that by the chiral borane-KH system. This implies that the step for the coordination of chiral organoborane to the hetero atom is important in the enantioselective reaction.

EXPERIMENTAL

The experimental techniques used in handling air-sensitive materials are described elsewhere.[7] Ir spectra were recorded on a Perkin-Elmer 1330 spectrophotometer using a two syringe technique.[7] ^{11}B Nmr spectra were recorded with a Bruker WP 80 SY spectrometer. ^{11}B Nmr chemical shifts were reported in ppm relative to BF_3 OEt_2. The alcohol products isolated by distillation were further purified through preparative GC using a 10% Carbowax 20M on Chromosob P colum (6 ft x 0.5 in.). The purity of alcohol products was confirmed by a analytical GC. Optical rotation was measured with a Jasco DIP-360 Digital Automatic Polarimeter.

Preparation of 9-OR*-9-BBNs, **1** and **2**. The procedure for the synthesis of 9-O-IPC-9-BBN (**1**) is representative. In an oven-dried 250-ml, round-bottom flask with a septum-capped sidearm and a reflux condenser connected to a gas burett was placed 150 ml of 0.5 M 9-BBN solution (75 mmol) in THF. To this stirred solution 12.2g (79 mmol) of (-)-isopinocampheol ($[\alpha]_D^{23}$ -34.1°, 95.5% ee)[8] was added dropwise to liberate hydrogen at room temperature and the mixture was stirred until the hydrogen evolution ceased. Evaporation of THF followed by distillation under vacuum gave 19g of pure **1** (69 mmol, 92.5%): bp 165-167°C/0.6 mm ; ^{11}B nmr (THF) δ 55.5 ppm. Similary, 91% yield of **2** was obtained: bp 198-201°C/0.5 mm ; ^{11}B nmr (THF) δ 56.3 ppm.

Preparation of K 9-OR*-9-BBNHs, **3** and **4**. The procedure for the synthesis of K 9-O-IPC-9-BBNH (**3**) is representative. An oven-dried 500-ml, round-bottom flask equipped with a sidearm was attached to a mercury bubbler. The flask was charged with 3g of oil-free potassium hydride (75 mmol) and 40 ml of THF. To this slurry, 13.7g (50 mmol) of **1** was added and the mixture was stirred vigorously for 2 h at room temperature. The hydride concentration of the resulting solution was measured by hydrolyzing an aliquot with a hydrolyzing mixture of THF-2 N HCl-glycerine (1:1:1). A 0.95 M concentration of **3** was observed: ir (THF) 2003 cm^{-1} (ν_{B-H}); ^{11}B nmr (THF) δ -1.52 ppm (a broad singlet).
Similarly, the 0.96 M THF solution of **4** was obtained: ir (THF) 2038 cm^{-1} (ν_{B-H}); ^{11}B nmr δ 1.3 ppm (a broad singlet).

Reaction of Racemic Epoxides with the 9-OR*-9-BBN-KH System. The following procedure for the enantioselective reduction of racemic 1,2-epoxyoctane with the **1**-KH system is representative. To an usual setup, 13.7g (50 mmol) of **1** in 30 ml of THF was charged and the solution was cooled to 0°C. And then 12.8g (100 mmol) of precooled 1,2-epoxyoctane was added at a time with vigorous stirring. The stirring was continued for 8 h at 0°C. The solution was transferred to oil-free KH (3g, 75 mmol) via a double-ended needle and the mixture was stirred vigorously for 7 h at 0°C. After the reaction completed, the unreacted 1,2-epoxyoctane was distilled and collected. The residue remained in the flask was hydrolyzed and oxidized with alkaline hydrogen peroxide in the usual manner. The aqueous layer was saturated with anhydrous K_2CO_3 and the separated organic layer was dried over anhydrous $MgSO_4$. The alcohol product was fractionated (85% yield) and further purified by a preparative GC. Finally, the optical rotation of pure product was measured: $[\alpha]_D^{22}$ -3.94° (neat), 39.8% ee in R.[4] From the reduction of 1,2-epoxyoctane collected from the reaction mixture with $LiAlH_4$, S-(+)-2-octanol in 39% ee was obtained[4]: $[\alpha]_D^{22}$ +3.87° (neat). The results are summarized in Table I.

Reaction of Racemic Epoxides with K 9-OR*-9-BBNHs, **3** and **4**. The reaction for racemic 1,2-epoxyoctane with **3** is representative. In the usual setup, the flask was charged with 52.6 ml of 0.95 M THF

solution of **3** (50 mmol) and the solution was cooled to 0°C. To this was added at a time 12.8g of precooled 1,2-epoxyoctane (100 mmol) and the mixture was stirred for 7 h at 0°C. The unreacted epoxide was distilled and collected. The residue was hydrolyzed and oxidized with alkaline hydrogen peroxide. The alcohol product was fractionated and purified as described above. The optical rotation of pure 2-octanol was $[\alpha]_D^{22}$ -3.68° (neat), 37.2% ee in R.[4]
The reduction of the unreacted 1,2-epoxyoctane provided (+)-2-octanol in 36.5% ee.[4] The results are summarized in Table III.

ACKNOWLEDGMENT : The authors in Yeungnam University thanks the financial support granted by Korea Science and Engineering Foundation.

REFERENCES

1. N.M. Yoon and J.S. Cha, Tetrahedron Lett., 1982, **23**, 5181.
2. J.S. Cha, K.W. Lee, and N.M. Yoon, Bull. Korean Chem. Soc., 1988, **9**, 62.
3. P.J. Leroux and H.J. Lucas, J. Am. Chem. Soc., 1951, **73**, 41.
4. (a) S.R. Landor, B.J. Miller, and A.R. Tatchell, J. Chem. Soc. (C), 1966, 2280.
   (b) S.R. Landor and A.R. Tatchell, ibid., 1967, 197.
5. P. Newman, P. Lutkin, and K. Milsow, J. Am. Chem. Soc., 1958, **80**, 465.
6. R.H. Pickard and J. Kenyon, J. Am. Chem. Soc., 1911, **99**, 45.
7. H.C. Brown, "Organic Syntheses via Boranes", A Wiley-Interscience Publication, New York, 1975.
8. G. Zweifel and H.C. Brown, Organic Syntheses, 1972, **52**, 59.

Received, 17th March, 1988